38. Overton, R. E. and M. E. DeBakey: Experimental Observations on the Influence of Hypothermia and Autonomic Blocking Agents on Hemorrhagic Shock. (In press)
39. Phillips, R. A., D. D. Van Slyke, V. P. Dole, K. Emerson, P. B. Hamilton and R. M. Archibald: Copper Sulfate Method for Measuring Specific Gravities of Whole Blood and Plasma (United States Navy Research Unit at the Hospital of The Rockefeller Institute for Med. Research), 1943–44.
40. Price, H. L., M. Helrich and E. H. Conner: A Relation Between Hemodynamic and Plasma Volume Alterations During General Anesthesia in Man. J. Clin. Invest., **35**: 125, 1956.
41. Reeve, E. B., M. I. Gregerson, T. H. Allen and H. Sear: Distribution of Cells and Plasma in the Normal and Splenectomized Dog and its Influence on Blood Volume Estimates with P^{32} and T-1824. Am. J. Physiol., **175**: 195, 1953.
42. Remington, J. W., W. F. Hamilton, H. M. Caddell, G. H. Boyd, N. C. Wheeler and R. W. Pickering: Vasoconstriction as a Precipitating Factor in Traumatic Shock in the Dog. Am. J. Physiol., **161**: 125, 1950.
43. Ricca, R. A., K. Fink, L. I. Katzin and S. L. Warren: Effect of Environmental Temperature on Experimental Traumatic Shock in Dogs. J. Clin. Invest., **24**: 127, 1945.
44. Scott, F. H.: Factors Influencing the Interchange of Fluid Between Blood and Tissue Spaces, I. Blood Pressure. Am. J. Physiol., **44**: 298, 1917.
45. Sherrington, M. A. and S. M. Copeman: Variations Experimentally Produced in the Specific Gravity of the Blood. J. Physiol., **14**: 52, 1893.
46. Starling, E. H.: On the Absorption of Fluids from the Connective Tissue Spaces. J. Physiol., **19**: 312, 1896.
47. Swan, H., I. Zeavin, J. H. Holmes and V. Montgomery: Cessation of Circulation in General Hypothermia. I. Physiologic Changes and Their Control. Ann. Surg., **138**: 360, 1953.
48. Owens, J. C., A. E. Prevedel and H. Swan: Prolonged Experimental Occlusion of Thoracic Aorta During Hypothermia. Arch. Surg., **70**: 95, 1955.
49. Walcott, W. W.: Blood Volume in Experimental Hemorrhagic Shock. Am. J. Physiol., **143**: 247, 1945.
50. Walcott, W. W.: Standardization of Experimental Hemorrhagic Shock. Am. J. Physiol., **143**: 254, 1945.
51. Wiggers, Carl J.: Physiology of Shock. Commonwealth Fund, New York City, 1950.
52. Wilson, J. N.: Unpublished data.
53. Wintrobe, M. M.: Clinical Hematology. Lea and Febiger, Philadelphia, 1946.

DISCUSSION.—DR. FIORINDO ANTHONY SIMEONE, Cleveland, Ohio: These observations which Dr. Wilson and his associates have reported are truly very interesting from a number of points of view. I have been particularly interested in the hemodilution and the promptness of the hemodilution that has been reported.

Dr. Cannon prepared a monograph on traumatic shock following observations in World War I. One of the observations which disturbed him most, I know, was that hemoconcentration was found in the soldiers who had been traumatized. He stated in his monograph that that phenomenon was unexplainable on physiologic grounds.

One might say, then, that the reverse would be easily explainable, and I think such is the fact. The hemodilution is readily explainable on the loss of pressure. The dynamics within the capillary where hemodilution and hemoconcentration must occur, are altered in the direction of preventing excess loss from the arterial end of the capillary, favoring absorption of fluid from the venous end of the capillary. Hence, hemodilution would occur, and it would occur very rapidly because there are miles of capillaries and the effect should be actually demonstrable in one circulation time. So, the rapid hemodilution is what one would expect.

More difficult to explain, I think, is the loss of that hemodilution in a matter of an hour and a half to two hours, if I recall the charts correctly. That is considerably more difficult to explain, because the blood pressure is being maintained while oligemia persists. It must be maintained by the same mechanism that was operating at first. That is, an increased peripheral resistance, an increased arteriolar tone, with decreased pressure within the capillary route.

So, I imagine some other mechanism other than vasoconstrictor mechanism must be operating in the loss of the hemodilution. Just what this is, I believe, must await further data. It would be interesting to know what the kidneys are doing during that two- or three-hour period. It is possible that some fluid may be lost through that avenue to lose the hemodilution which had occurred very early.

I want to congratulate the authors for this truly excellent piece of work.

DR. FRANCIS D. MOORE, Boston, Massachusetts: I would also like to congratulate the essayists on a beautifully simple, clear demonstration. I would like to add one bit of information, and ask two questions.

We have been interested in the effects of hemorrhage in normal man, and these studies have been done as part of our program of trying to understand the various components of the surgical experience. In normal human volunteers we have produced hemorrhages which are from the venous side of the circulation and slightly larger than a blood donation. They are in the 800 cc range. They are non-shock producing, which of course is different from this situation. Naturally, they are normothermic. It was of interest to us that in our experiences we find the rate of transcapillary movement of fluid in response to this vascular stress, if one can call it that, to be extremely variable. Some of our subjects have started to hemodilute during the hemorrhage, as Dr. Wilson and Dr. Swan's dogs did, but others have been very slow, taking 12 to 18 to 20 hours to complete their initial hemodilution, which we thought was of interest with respect to the evaluation of hematocrit and hemoglobin readings after hemorrhage. We have not observed in man, in these lesser volume losses, a redistribution back from the blood stream to the interstitial fluid.

I have two questions. If I remember the first slide correctly, the survival rates in the 31° to 26° temperatures were not very different from normothermic dogs. It was the very cold dogs, with temperatures down to 26° and 20°, that did not do so well. I wonder what the mortality is in dogs that are just cooled down to the 20°–26° level without anything further being done. I also wonder if Dr. Wilson and his group have taken the next step as yet, that of producing the shock-like state first, and then cooling the dog, which might be more what one might do in treating shock with hypothermia.

Dr. Michael E. DeBakey, Houston, Texas: I, too, want to express my pleasure in listening to this presentation. I am also pleased to see another group of investigators interested in this particular problem, that is, the effect of hypothermia upon shock. We have been interested in this problem and have submitted a report of some of our preliminary observations on the effect of hypothermia on experimental hemorrhagic shock in the dog, using the preparation that Fine has employed for his studies. The reason we used this preparation was because we had previously had considerable experience with it in the evaluation of chemotherapy in shock.

Unlike that preparation, however, in which it was unnecessary to use general anesthesia, this became a requirement in its application to the hypothermic experiment, thus altering the experiment somewhat since it added further stress. In partial answer at least to one of the questions Dr. Moore raised, I might say that under controlled conditions, in which only anesthesia and hypothermia were used, there was a mortality rate of 10 per cent.

We began our studies in a different way, and therefore they are not entirely comparable with the studies that Drs. Wilson, Swan and their associates have reported. They began with a preparation which produced no mortality. On the other hand we began with a preparation that produced a high mortality, averaging well over 90 per cent. Therefore, if there was going to be any effect with the use of any agent, hypothermia being one of the agents we used, it almost had to be in the form of benefit because these animals could not have gotten much worse.

(Slide) The results of our observations are shown on these slides. In addition to hypothermia, we used chlorpromazine. Here you see the results of the use of the various agents, cooling being shown in this chart as compared with the controls. These data suggest that some benefit is derived from using cooling alone. I might say these animals were cooled only to 31° in contrast with the lower temperatures which Dr. Wilson and his associates employed. Better results, however, were obtained with the use of chlorpromazine and the combined use of chlorpromazine and cooling.

(Slide) This next slide shows the additional observations that were made, which would suggest that when hypothermia was used alone at this moderate degree, there was not a great deal of difference between these animals and the controls in terms of duration of hypotension, maximum bleeding volume, and time to reach maximum bleeding volume.

However, when chlorpromazine was used there was an alteration produced, in the sense that it took longer to bleed these animals to the maximum amount, and the maximum amount of bleeding was less than in the controls and the hypothermic animals. To that extent there was some alteration in the experiment by the addition of chlorpromazine.

Since our experiments differed from those reported by Dr. Wilson and his associates, it is difficult to determine the reasons for the apparently conflicting conclusions concerning the effect of hypothermia on experimental hemorrhagic shock.

Dr. Philip Sandblom, Lund, Sweden: I should have come up here before, because this subject is one of the things I know the least about; but I might tell you that in our laboratory Dr. Gelin has been interested for several years in the aggregation of the red corpuscles, and he found that one of the states in which he finds the highest degree of sludge or aggregation is in hypothermia, especially when the hypothermia reaches low levels between 26° and 28° Centigrade.

I should like to ask Dr. Wilson whether he thinks that this might have some bearing on his work, and perhaps, with the hematocrit being lowered because of the aggregation, whether this might interfere with the results.

Dr. Robert Dunning Dripps, Philadelphia, Pennsylvania: Perhaps one can resolve Dr. DeBakey's and Dr. Swan's experiments by pointing out that no one has yet been able to extract from

an animal or from man the same volume of blood over the same time course either during the actions of the ganglionic blocking agents, hypothermia or any of the other alleged protective mechanisms.

We shall in all probability not find a single physiological explanation for this, but rather that multiple factors will be involved. One, for example, is the inability of the veseels to constrict in response to hypotension. This is minimized by the ganglionic blocking drugs, and is also minimized with reduction in central nervous system reactivity by cooling, the degree of reduction of compensatory constriction being presumably related to the degree of temperature reduction.

Another factor perhaps related to the comments of Dr. Sandblom and neglected by many of us in the field of hypothermia, concerns the aspects of blood viscosity, the increasing amount of viscosity interfering far more than we anticipate.

The experiments described by Dr. Wilson are of value for those who would believe that under hypothermia one can protect the surgical patient to greater degrees than is actually possible. Hypothermia is not a panacea.

I enjoyed thoroughly this presentation, and regard it as being of the utmost importance.

DR. HENRY SWAN II, Denver, Colorado: I would like to recall to your minds that there were many names attached to this paper; it certainly does represent a group endeavor. We are all wound up in this work, and many people participated very actively in it. I would like to make one or two comments in regard to the discussers and I would first like to thank them all for their very kind remarks.

Dr. Simeone, we also don't attempt to explain the mechanism regulating the loss of the dilution fluid. We were very unprepared to find it going back so rapidly in these experiments. I had always thought that the dilution fluid was an important part of the mechanism which held up the blood pressure following hemorrhage and yet, from these experiments, we felt that we had no evidence to substantiate this common point of view, and we do not know why the fluid goes back to the extravascular spaces.

Dr. Moore's comments were very pertinent. In regard to the dilution which occurs following the removal of blood in man, you will recall that Dr. Baumgartland has also shown that there is a rapid and often persistent dilution; but in his report, which was a study of blood donors, there was no report made of the blood pressure response of these individuals. I would like to turn that question back to Dr. Moore. What happened to the blood pressure of these patients in whom you were withdrawing the blood? Our present feeling is that if there was not much blood pressure response, it would be hard to predict about the dilution.

You are quite right about the middle degrees of hypothermia. Only one animal died in the middle group. In our laboratory, the mortality rate of cooling a dog to 20° or 22° using hyperventilation is less than 3 per cent. In other words, cooling an animal to this degree and then warming it up again does not carry a very significant mortality rate if the animal has its respiration supported.

We also quite agree with Dr. Moore that the immediate and obvious thing to do is to have the hemorrhage or the stress come first, and then study the effect of hypothermia on that. We certainly thank him for the suggestion.

Dr. DeBakey brings up the question of anesthesia. Because this is so important, Mr. President, I would like, with your permission, to show just one slide in regard to the problem of anesthesia.

(Slide) It has been suggested by some that pentobarbital blunts the response as far as fluid shifts are concerned following hemorrhage. Corcoran and Page have shown that, by and large, it raises the blood pressure.

Here is a group of animals under anesthesia and another group of unanesthetized animals. In some we used morphine and ether. Notice that the pre-hemorrhage blood pressure in group with pentobarbital is considerably higher than the mean pre-hemorrhage blood pressure in any other group. Starting from the first blood pressure, after the animals were bled 35 per cent the pentobarbital group had a fall of 85 mm, whereas the others had a fall only half as great. Interpreting the actual measured amount of plasma dilution, the animals in this group had a considerably greater amount of fluid shift than the animals in the other groups.

So, we feel that pentobarbital definitely does affect the experiment; and, secondly, it may do it by virtue of the fact that the blood pressure drop is greater. This merely means, however, that pentobarbital does not blunt the process we are studying; far from it, it may actually accentuate it.

Dr. Sandblom, we thank you very much for your comment. We certainly agree with you and Dr. Bigelow and others, and Dr. Hegnaur, who have shown that blood is trapped and red cells are agglutinated. Certainly there is a great variability in hematocrit during cold. This is one of the important things, we think, in the use of iodinated serum technique, because this tags the albumin, and hence you can measure the dilution of tagged albumin. In our work this phenomenon was seen, and will appear in the paper, namely, that during cold there appeared to be fewer red blood cells available for dilution than there was albumin available for dilution, which is another way of saying exactly what you stated.

I also want to thank Dr. Dripps for his comments. The removal of blood was accomplished uniformly in all animals by a large catheter in the aorta, and the measured volume of blood was removed in between three and six minutes. So, we attempted to achieve rapid uniform removal as much as possible.

Once again, thank you all for your comments.